A new target for myeloma therapy

Rauf Haznedar Gazi University Medical School

In this issue of Blood, Azab and colleagues demonstrate that PSGL-1 expressed on myeloma cells is involved with regulating tumor cell extravasation, homing, disease progression, and drug resistance.1

Over the past two decades, treatment for multiple myeloma has improved with the use of high-dose melphalan therapy with peripheral blood stem cell support and novel drugs including thalidomide, bortezomib, and lenalidomide. In younger patients, survival now extends beyond 10 years. In elderly myeloma patients, obtaining complete remission has become the goal of therapy with the use of novel drug combinations. Myeloma cell–microenvironment interactions are crucially important in understanding disease biology and pathogenesis.2 After the discovery of IL-6, we have learned that insulin–like growth factor–1, vascular endothelial growth factor, and tumor necrosis factoralpha also promote myeloma cell proliferation. Microenvironment bone marrow stroma not only contribute to myeloma cell growth and survival, but also produce proangiogenic factors and contribute to drug resistance and bone disease.2,3 Proteasome inhibitors and the immunomodulatory drugs (ImiDs) thalidomide and lenalidomide affect the microenvironment in addition to directly killing myeloma cells. ImiDs enhance immune response to myeloma cells, enhance natural killer cell function, stimulate T-cell proliferation and CD8+ T-cell activation, and increase IL-2 and IFNγ levels.4 Bortezomib suppresses the expression of CD49d at mRNA level, down-regulates VLA-4, and may help overcome cell adhesion–mediated drug resistance.1 Bortezomib inhibits osteoclastogenesis and stimulates bone formation. It can be used in combination to treat myeloma bone disease.

Despite these advances, multiple myeloma is still an incurable disease. Myeloma patients, having worse genetic features, have poorer response to therapy and survival is short. Apart from the reported high-risk features, cell adhesion–mediated drug resistance plays a role in treatment failure. Although the proteasome inhibitor bortezomib helps overcome drug resistance to some extent, we clearly need new approaches.

Targeted therapy with monoclonal antibodies has given rise to great hope in hematologic malignancies. We need to develop more effective drugs and more efficient antibodies. Currently targeted therapy with cyclin-dependent kinases4/6 and VEGF receptor-3 inhibitors and Hedgehog signaling blockade are in preclinical testing.5,6 Different and possibly more specific molecular, immunologic, and genetic targets are needed for further progress in the treatment of multiple myeloma.

Here, Azab et al demonstrate the importance of the P-selectin glycoprotein ligand–1 (PSGL-1) and P-selectin axis in myeloma pathobiology and disease progression. PSGL-1 is a cell-surface glycoprotein expressed on leukocytes and is a principal ligand for selectins, mediating rolling of leukocytes on endothelium. PSGL-1 is a plasmacytic differentiation marker in both normal and neoplastic plasma cells and has been considered a potential target for antimyeloma therapy.2,8 Azab et al for the first time elegantly demonstrate both in vitro and in vivo that PSGL-1 together with P-selectin regulates adhesion of MM cells to BM stroma and are important in transendothelial migration (see figure). PSGL-1 and P-selectin are responsible for myeloma cell adhesion, homing, and tumor progression. Moreover, PSGL-1 is involved in tumor initiation and drug resistance. Azab et al also demonstrate PSGL-1 gene expression increases as the disease progresses from MGUS to advanced stages of myeloma. This makes PSGL-1 a reasonable target for treatment in resistant and advanced...
cases of multiple myeloma. Interestingly, PSGL–1– P-selectin interaction leads to adhesion–related cell signaling and activation of integrins, although Azab and colleagues did not address integrin–selectin interaction in their study. Prior studies have shown that myeloma cells through αβ1 integrin and VLA–4 molecules bind to bone marrow stroma (VCAM–1 and fibronectin). To understand myeloma cell trafficking, adhesion, homing, and drug resistance better, future studies on the interaction of integrins and selectins seem necessary.

Although significant advances have been obtained, we are far from delineating the myeloma progenitor cell. We still do not know the exact nature of myelomagenesis and the primary genetic event. Finding new treatment options for genetically high–risk patients will obviously depend on progress in genomics.

Plasmacytic dendritic cells have been shown to be responsible for growth, survival, and drug resistance as well as immunodeficiency in myeloma. Another targeting point seems to lie in interactions between myeloma cells and plasmacytic dendritic cells.

Myeloma bone disease is another very important problem. Bone disease is very much related to MM cell–microenvironment interaction because RANKL/RANK cross-talk also enhances osteoclast formation and bone resorbing activity. Monoclonal antibody to RANKL and recombinant OPG with or without biphosphonate therapy has been used in the treatment of bone disease. Myeloma cells secrete soluble Dickkopf–1 protein that inhibits osteoblast precursors. Anti–Dickkopf–1 monoclonal antibody is very promising in phase I/2 trials. Combination therapy with newer drugs, immunotherapy, and bone healing agents together will take us closer toward the cure.

Conflict–of–interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Hay and DiMichele, page 1335

Getting rid of refractory hemophilia

Pier Mannuccio Mannucci IRCCS CA’ GRANDA MAGGIORE POLICLINICO HOSPITAL FOUNDATION

In a prospective randomized, multicenter study of immune tolerance induction (ITI) in patients with hemophilia A refractory to replacement therapy after the development of alloantibodies that inhibit factor VIII (FVIII) activity, Hay and DiMichele compared two regimens, a low dose of FVIII (50 IU/Kg thrice weekly) or a high–dose (200 IU/kg daily). These therapeutic regimens have reported to induce a similar overall success rate (roughly two-thirds of patients responding as defined by inhibitor disappearance and normal plasma FVIII half-life and recovery). This study, which enrolled patients from 17 countries on 4 continents, contributes data that should help define an evidence–based practice of ITI. It also stands as a milestone because it shows that investigator–driven, randomized clinical trials can be carried out and completed even in rare diseases such as hemophilia without the direct involvement of the pharmaceutical industry.

How to eradicate FVIII inhibitors and successfully treat the most challenging complication of hemophilia has been a long–standing issue. As early as 1977 Brackmann and Gormsen reported that, in a patient with severe hemophilia A, a long–standing, high–titer inhibitor disappeared completely by infusing high daily doses of FVIII for a prolonged period of time. This striking and puzzling observation, which led to the development of the so–called Bonn ITI regimen (that broadly corresponds to the high–dose regimen evaluated by Hay and DiMichele) was received with skepticism by the hemophilia community. The reasons for the skepticism were multiple: lack of an experimental basis for this novel approach; limited knowledge on FVIII immunology; the substantial cost of the huge FVIII dosages employed at a time when therapeutic coagulation factors still had limited availability; the challenges put on patients’ resilience and venous access by daily or twice–daily factor infusions; and the fear of transmitting viral hepatitis and then later, HIV infection. Nevertheless, the persistent and unswerving efforts of the Bonn group to confirm and extend the original case report led to several small, non–randomized cohort studies that confirmed that flooding the immune systems of these patients with the antigen (FVIII) did quench the production of the neutralizing antibody with a success rate ranging from 63% to 80%.

How did studies subsequently advance on clinical implementation of ITI? Cognizant of the difficulties implicit in the interpretation of retrospective data from small cohorts of patients with a rare complication of a rare disease, some clinicians chose to gather and analyze data from registries. The International, German, and North American registries obtained broadly consistent results on the variables that influence ITI outcome. The main predictors of success were low inhibitor peaks, low inhibitor titers before ITI start, and low anamnestic peaks after start. These factors provide clinicians with crucial information to select the most suitable patients for this expensive and demanding treatment.
A new target for myeloma therapy

Rauf Haznedar